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October 14, 1999

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 99D-2635; Notice/Draft Guidance for Industry on ANDA's: Blend Uniformity Analysis, *Federal Register/ Vol. 64, No. 166, August 27, 1999*

Dear Sir or Madam:

Bristol-Myers Squibb (BMS) is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1998, pharmaceutical research and development spending totaled $1.4 billion.

We are very interested in and well qualified to comment on this FDA proposal intended to provide recommendations to holders of abbreviated new drug applications (ANDA's) on establishing in-process acceptance criteria related to blend uniformity analysis (BUA) for the manufacture of some drug products.

Summary of BMS's Comments

We commend the U.S. FDA for the issuance of this guidance document. However, we do not agree that a need exists for routine BUA testing; further, and for the reasons cited below, we find blend uniformity analysis superfluous, cost ineffective, time consuming, and of little or no value added in a validated manufacturing process. Specifically, and corresponding to the same headings in the guidance document our comments are:

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I. INTRODUCTION

- While a useful tool for process development, blend uniformity analysis (BUA) is not an appropriate application as a routine in-process test. BUA testing is performed during product and process development, scale up and on through validation to establish confidence in the reliability and repeatability of the process. Routine BUA following validation renders the validation activity hollow and meaningless. The patient consumes the finished dosage form and not in-process blends. Specific statistical correlation between BUA and finished dosage uniformity is rarely established due to the additional handling and movement of powders during subsequent unit operations.

II. SCOPE

- The list of products includes coated tablets (other than film coated tablets), transdermal systems, suspensions (in single-unit containers or in soft capsules), pressurized metered-dose inhalers, and suppositories but does not include other common dosage forms such as uncoated tablets, capsules, multi-dose powders for oral suspension.

- BUA should not be conducted as an in-process test on commercial batches of product. Successful BUA performed during process validation obviates the need for routine BUA in commercial manufacturing. After process validation, finished product Content Uniformity (CU) testing is sufficient to confirm satisfactory processing of the batch.

- As noted in the draft, 21 CFR 211.110(a)(3) calls for assuring adequacy of mixing to ensure uniformity. Adequacy of mixing is demonstrated during process development and validation, while routine finished dosage testing provides continued assurance of both the uniformity of the product, but is also indicative that the mixing process was conducted as previously and satisfactorily validated.

- Routine BUA presents no quality enhancement to the finished product and creates extreme time, material, and manpower burdens on manufacturing and Quality Control operations.

III. SAMPLING SIZE AND PROCEDURES

- Adjusting the sample size for sample bias should include both high or low bias. The guidance only refers to low bias.

- The second paragraph of this section notes the BUA as an in-process control. This statement should be deleted.

- BUA for bioequivalence batches, especially if not performed in a commercial facility, have little utility because the manufacturing process typically undergoes further modifications in scale, equipment, and parameters prior to validation.

IV. ACCEPTANCE CRITERIA AND ANALYTICAL PROCEDURES

- Eliminate the reference to commercial batches in the first paragraph.

- BUA individual sample limits are not indicated. They should be the same as USP Content Uniformity standards (85%-115%; RSD NMT 6%) due to the inherent potential for error introduced by the blend sampling procedure.

- Since the USP Content Uniformity limits are endorsed for BUA, Stage 2 testing should not be deleted. Inherent variability of blend sampling procedures and sample handling requires the option of performing Stage 2 testing.

- The guidance points out that uniformity may be compromised in subsequent steps following validation as justification for the arbitrarily tighter than USP 5% RSD limit. The guidance ignores the fact that additional processing steps can and in fact usually do improve uniformity. In addition, as previously stated, blend uniformity sampling technique is more variable than individual finished dosage forms.

BMS appreciates the opportunity to provide comment and respectfully requests the FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

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